British Journal of Pharmacy

https://doi.org/10.5920/bjpharm.1402

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Proceedings of the 14th APS International PharmSci 2023

Subcutaneous Biopharmaceutics: Building Tools for a Flexible Future

Kate Harris[a], Laura Gonzalez-Garcia[a], J. Matthew Wood[a], Iain Grant[b], Simon Todd[b],

[a]New Modalities and Parenteral Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield, UK

[b]Innovation Sciences and External Liaison, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield, UK

ARTICLE INFO

Received: 30/07/2023
Accepted: 08/08/2023
Published: 30/12/2023

*Corresponding author.
Tel.: +44 (0) 7760 165263
E-mail:
kate.harris@astrazeneca.com

KEYWORDS:
Biopharmaceutic tools, Subcutaneous administration, PBBM, safe space

SUMMARY

The major biopharmaceutics challenge faced during the development of subcutaneous (SC) drug products is the limited understanding of the physiological factors and the combination product attributes that can impact absorption rate/extent and drug product performance. Currently, the biopharmaceutics toolkit available to characterize and predict SC in vivo performance is immature compared to that of oral delivery, resulting in conservative bioequivalence (BE) strategies and costly clinical studies to manage even modest drug product changes during clinical development. This abstract summarises the development of novel SC Biopharmaceutics tools, the approaches we are taking to characterise and predict SC drug product performance and the questions we would still like to investigate. We are pursuing a strategy centred on a best-in-industry in silico model, and driving improvements in dosing characterisation and in-vitro methods to build holistic understanding.

INTRODUCTION

Subcutaneous (SC) delivery is an important route of administration for new molecular entities such as peptides, antisense oligonucleotides or antibody drug conjugates to improve patient compliance and outcomes.

The major biopharmaceutics challenge faced during the development of SC drug products is the limited understanding of the physiological factors and the combination product attributes that can impact the rate and extent of absorption and overall drug product performance.

Currently, the biopharmaceutics toolkit available to characterize and predict SC in vivo performance is immature compared to that of oral delivery, resulting in conservative bioequivalence (BE) strategies and costly clinical studies to manage even modest drug product changes during clinical development.

Our ambition is to identify, evaluate and implement transformative science and technology to establish an industry-leading predictive capability for SC drug products, with the same level of regulatory impact as available in oral delivery.

To realise this vision, three approaches are being actively developed: 1) A best-in-industry digital tool (SubQ-Sim) to predict SC drug product performance, 2) A combination drug product safe space developed through enhanced injection characterisation and 3) novel in vitro tools to provide mechanistic insight of SC administration.

https://doi.org/10.5920/bjpharm.1402

SUBQ-SIM DIGITAL TOOL

We have built a new fully mechanistic software modelling tool, SubQ-Sim to improve our capability above currently available tools. We have built this based on detailed knowledge of the underlying physics of fluid exchange in the SC space, the relevant physical chemistry and DMPK of the absorption and mass transport processes, and the physiological structure of the adipose tissue.

The software can predict the overall shape and drug concentrations of the depot formed following a SC dose and predicts how this will evolve over time and influence distribution, leading to human plasma PK predictions.

Development of the tool continues in response to user testing in projects and parallel research and development.

INJECTION DYNAMICS CHARACTERISATION

To optimise our in-house, best-in-industry, in silico tool (SubQ-Sim) for simulation of SC drug delivery, and develop an injection safe space bridging approach, ex vivo and in vivo evaluation of a Finger Tactile Pressure Sensing (Finger TPS™) system is in progress in order to quantify injection dynamics, specifically force and rate of injection.

The tool will be eventually deployed in a clinical setting to seek to establish a combination drug product safe space.

IN VITRO CHARACTERISATION OF FIRST PASS SC METABOLISM

Characterisation techniques to understand and quantify first-pass SC metabolism and SC protein binding are currently lacking. This data has the potential to improve bioavailability and absorption rate predictions of SC administered products and provide crucial input data for SubQ-Sim.

Subcellular fraction characterisation from porcine SC homogenates are currently being evaluated for the study of metabolic clearance and protein binding.

CONCLUSIONS

Our capability build in SC biopharmaceutics aims to increase the mechanistic understanding of this poorly understood route of administration to enable the development of novel modelling tools and in-vitro techniques that will enable the development of smarter SC formulations. This holistic approach will expand our knowledge of the injection, absorption, distribution and metabolic processes that govern the SC administration route. There is a clear opportunity for broad collaboration across industry and academia to advance the development and validation of these novel SC models.

ACKNOWLEDGEMENTS

Xavier Pepin, Simulations Plus and Pressure Profile Systems, UK Ltd.